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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 03/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/995,452	BENVENISTY ET AL.	
	Examiner	Art Unit	
	Thai-An N Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-56* is/are pending in the application.

4a) Of the above claim(s) *18-35 and 37-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17, 36 and 48-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' Amendment, filed 12/22/03 has been entered.

Claims 1-56 are pending. Claims 18-35 and 37-47 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 13.

Claims 1-17, 36 and 48-56 are under current examination.

Claim Objections

The prior rejections of claims 17 and 56 are withdrawn in view of Applicants' amendments to the claims.

Election/Restrictions

This application contains claims 18-35 and 37-47 drawn to invention(s) nonelected with traverse in Paper No. 13. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The prior rejection of claim 48, is maintained. The claim recites that in the human ES cells modified by *foreign* DNA, the DNA is only expressed by selected *derivative* cells or *derivative* cells. Firstly, the term "foreign" is unclear. For example, is the DNA from another species? Applicants argue that the term *foreign* is clear in the context of the claim and that the recitation of the term "exogenous" may contradict language which states that the DNA, "occurs in the embryonic stem cells but is not expressed in them at levels which are biologically significant." This is unclear, because it appears that foreign DNA that occurs in ES cells but is not expressed in them in biologically significant levels would appear not to be foreign, but endogenous to the claims. Claims 49-56 depend from claim 48.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The prior rejection of claims 1-4, 6, 10, 36, 48-56 under 35 U.S.C. 102(a) or 35 U.S.C. 102(e) as being anticipated by Smith *et al.* is maintained for reasons of

record. The prior rejection of claims 11-13, 15 and 16 is withdrawn in view of Applicants' amendments to the claims with the deletion of the term "by electroporation".

Applicants argue that the pending claims are drawn to novel features that are not taught by the cited art. Firstly, Applicants argue that claims 36 and 48-56 are not anticipated or obvious over the cited art because the cited art fails to enable the creation of the claimed subject matter because the transfection techniques of the cited art are too low to create the claimed cell populations. Applicants point to the examples of Smith *et al.* who use electroporation techniques to insert DNA into murine ES cells, and then cite Zwaka and Thomson to show that murine electroporation protocols to insert DNA into hES cells are ineffective. Applicants argue that Smith states without showing that injection, lipofection, transfection and infection with a viral vector may be used to transfect ES cells, but the reference provides no showing that these techniques enable transfection into human ES cells at rate substantial enough to create the claimed cell populations, and thus, Smith cannot anticipate the claims because they are drawn to "substantially pure" or "reagent cell populations". See pp. 12-13 of the Response. Applicants further argue that none of the cited art provides a successful protocol for transfection of human ES cells and the lack of any previous protocol for DNA transfection into human ES cells underscores that murine ES cell techniques cannot be assumed to work with human ES cells. For example, electroporation, which may be a successful

transfection technique with murine ES cells has extremely poor efficiency when applied to human ES cells. Applicants argue that the differences between mouse and human ES cells and thus, techniques that succeed in mouse ES cells cannot be expected to be successful for human ES cells. Applicants conclude that Smith cannot anticipate any of the pending claims because the reference only enables its techniques for mouse ES cells, and not human ES cells. See pp. 14-15 of the Response.

This is not found to be persuasive. The methods as taught by Smith anticipate the claimed invention because they teach every element recited in the claims, and thus the products produced by Smith would also anticipate the claimed invention. Thus, the teachings of Smith fulfill the requirements under 35 U.S.C. § 102. Applicants' arguments that the methods as taught by Smith would not produce sufficient cell populations are not pertinent to the instant claims. The claims do not require a particular number, concentration or percentage of cells, that are transfected by the polynucleotide of interest, or a particular transfection efficiency. For example, two hES cells that are transfected with the polynucleotide would be sufficient to anticipate the claimed invention. Furthermore, Applicants' arguments that the cited art is not enabling is not persuasive because Applicants have failed to provide evidence or teachings to show that the methods as taught by Smith would not result in the transfection of human ES cells. It is reiterated that that the claims encompass one hES cell transfected by the method. Note further

that the instant specification supports that electroporation can result in the transfection of hES cells. See p. 11, line 30-33. Accordingly, it is maintained that Smith anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The prior rejection of claims 5 and 14 under 35 U.S.C. 103(a) as being unpatentable over Smith *et al.* as applied to claims 1-4, 6, 8-13, 15, 16, 36 above, and further in view of Myers is *maintained* for reasons of record.

Applicants argue that the cited art of Smith may state that some of its techniques are applicable to humans, but the data provided by the examples of Smith are only directed to mouse ES cells. Thus, Applicants argue that the lack of previous protocol for DNA transfection in hES cells and the differences between mouse and human ES cells would show that one of skill in the art would not expect that the same techniques would work in human ES cells as mouse ES cells.

This is not found to be persuasive. For example, Applicants have provided the post-filing art of Zwaka and Thomson to show that using a typical mouse ES cell protocol to transfect human ES cells yielded a stable transfection rate of 10^{-7}, which Applicants quote as being, "too low to be practical for identifying rare homologous recombination events." See pp. 14-16 of the Response. It is reiterated that the instant claims are rendered obvious over the cited art of record, because it would be obvious for one of ordinary skill in the art to utilize the methods of transfecting stem cells, as taught by Smith and transfect a construct encoding a fluorescent protein, such as Rennila protein, or luciferase, with a reasonable expectation of success. Zwaka and Thomson support that utilizing methods of electroporation for transfection would result in some hES cells being transfected, and the claims encompass even one hES cell transfected with such a construct, therefore

Applicants' arguments with regard to the "practicality" of the methods is not relevant to the instant rejection.

Accordingly, in view of the combined teachings of Smith and Myers, it would have been obvious for one of skill in the art to utilize the methods of transfecting stem cells, as taught by Smith, and transfect a construct encoding a fluorescent protein, such as Rennila protein, or luciferase, with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification, as it was well-known in the art to use such fluorescent proteins as reporter genes and various other assays, and as supported by Myers, "Bioluminescent reactions are used as analytical tools in protein and nucleic acid blotting, in nucleic acid sequencing and hybridization assays, and in reporter gene studies ... The main advantages to these reactions are their simplicity and analytical sensitivity." See p. 165, 2nd column, 1st ¶.

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear and convincing evidence to the contrary.

With regard to claims 7 and newly amended claims 11-17, and the rejections of the claims thereof, Applicants argue unexpected results using cationic polymer reagents to transfect hES cells. Applicants direct the Examiner to the specification and Figure 1, which shows an increase in the relative activity for a transfected gene

compared to other transfection techniques. Applicants argue that the combination of Fasbender and Smith cannot support the obvious rejection because Fabender provides no teaching with regard to the unexpected superiority of cationic polymer reagents in transfecting human ES cells. Applicants argue that Fasbender actually teaches away from the unexpected benefits of cationic polymer reagents by first showing an improvement in gene transfer using cationic lipids or polymers, and that Fasbender does not show its techniques with regard to ES cells. Moreover, Applicants argue that Fasbender actually points away from a reasonable expectation of success because the reference requires the presence of an adenovirus vector with the cationic vector to catalyze gene transfer and the instant claims do not require an adenovirus vector. See pp. 10-12 of the Response.

Applicants' arguments are not persuasive. Note that the claims are silent with regard to the presence or the absence of an adenovirus vector. Furthermore, the scope of the claims is not commensurate with the unexpected result(s). The specification teaches that teaches a particular cationic polymer, Exgen, which provides Applicants' unexpected result. However, the claims broadly read on any cationic polymer, the breadth of which may or may not produce Applicants' unexpected results. It is reiterated that because the claims do not require do not require particular transfection efficiency, a number, percentage or concentration of cells that are transfected by the claimed method, the cited art of Smith and Fasbender render the instant claims obvious.

Thus, the prior rejection of claim 7 and newly amended claims 11-16 is maintained under 35 U.S.C. 103(a) as being unpatentable over Smith *et al.* as applied to claims 1-4, 6, 8-13, 15, 16, 36, 48-56 above, and further in view of Fasbender *et al.* because the claims only require the transfection of a hES cell, and as stated by Applicants in the Response [see, for example, p. 15, 2nd ¶] that an hES cell could be transfected, even with poor efficiency. Thus, it is maintained that in view of the combined teachings of Smith and Fasbender, it would have been obvious for one of ordinary skill in the art to utilize the method of stem cell transfection, as taught by Smith, by utilizing a cationic non-lipid polymer reagent, such as the poly-L-lysine hydrobromide polymers taught by Fasbender, with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification, as it was art-recognized to optimize gene transfer techniques, as supported by Fasbender who state that, "[T]he complexes of adenovirus and cationic molecules increase the efficiency of gene transfer." See Abstract.

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear and convincing evidence to the contrary.

Claim 17, as amended, is rejected under 35 U.S.C. 103(a) as being unpatentable under 35 U.S.C. 103(a) as being unpatentable over Smith *et al.* , and

further in view of Fasbender *et al.* and further in view of Pascolo *et al.* is *maintained* for reasons of record.

Applicants argue unexpected results using cationic polymer reagents to transfect hES cells. Applicants direct the Examiner to the specification and Figure 1, which shows an increase in the relative activity for a transfected gene compared to other transfection techniques. Applicants argue that the combination of Fasbender and Smith cannot support the obvious rejection because Fabender provides no teaching with regard to the unexpected superiority of cationic polymer reagents in transfecting human ES cells. Applicants argue that Fasbender actually teaches away from the unexpected benefits of cationic polymer reagents by first showing an improvement in gene transfer using cationic lipids or polymers, and that Fasbender does not show its techniques with regard to ES cells. Moreover, Applicants argue that Fasbender actually points away from a reasonable expectation of success because the reference requires the presence of an adenovirus vector with the cationic vector to catalyze gene transfer and the instant claims do not require an adenovirus vector. See pp. 10-12 of the Response.

Applicants' arguments are not persuasive. Note that the claims are silent with regard to the presence or the absence of an adenovirus vector. Furthermore, the scope of the claims is not commensurate with the unexpected result(s). The specification teaches that teaches a particular cationic polymer, Exgen, which provides Applicants' unexpected result. However, the claims broadly read on any

cationic polymer, the breadth of which may or may not produce Applicants' unexpected results. It is reiterated that because the claims do not require do not require particular transfection efficiency, a number, percentage or concentration of cells that are transfected by the claimed method, the cited art of Smith, Fasbender and Pascolo render the instant claims obvious.

Accordingly, in view of the combined teachings, it would have been obvious for one of ordinary skill in the art to utilize the method of stem cell transfection, as taught by Smith, by utilizing a cationic non-lipid polymer reagent, such as the poly-L-lysine hydrobromide polymers taught by Fasbender, to knockout a genomic sequence, such as beta-2 microglobulin, as taught by Pascolo, with a reasonable expectation of success. One of ordinary skill would have been sufficiently motivated to make such a modification, as it was an art-recognized technique to knock-out endogenous genes to analyze gene expression and, and that in generating the double knockout H-2D^{b} /mouse beta2 microglobulin, Pascolo states, "This should facilitate the study of HLA class I-restricted responses compared to classical transgenic mice. One might home that the information gained with these animals will be of human relevance." See p. 2050, 2nd column, lines 4-7.

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear and convincing evidence to the contrary.

The prior rejection of claims 8 and 9 under 35 U.S.C. 103(a) as being unpatentable over Smith *et al.* as applied to claims 1-4, 6, 8-13, 15, 16, 36, 48-56 above, and further in view of the Gibco BRL catalog is *maintained* for reasons of record.

Applicants' arguments with regard to this rejection is directed to the art of Smith. Particularly, that Smith cannot anticipate any of the pending claims because the reference is only enabling for its techniques for murine ES cells, and not human ES cells, as required by the claims. Thus, Applicants argue that the lack of previous protocol for DNA transfection in hES cells and the differences between mouse and human ES cells would show that one of skill in the art would not expect that the same techniques would work in human ES cells as mouse ES cells.

This is not found to be persuasive. For example, Applicants have provided the post-filing art of Zwaka and Thomson to show that using a typical mouse ES cell protocol to transfect human ES cells yielded a stable transfection rate of 10^{-7}, which Applicants quote as being, "too low to be practical for identifying rare homologous recombination events." See pp. 14-16 of the Response. It is reiterated that the instant claims are rendered obvious over the cited art of record, because the claimed methods do not require do not require particular transfection efficiency, a number, percentage or concentration of cells that are transfected by the claimed method. Furthermore, Zwaka and Thomson, cited by Applicants, support that utilizing

methods of electroporation for transfection would result in some hES cells being transfected, and the claims encompass even one hES cell transfected with such a construct, therefore Applicants' arguments with regard to the "practicality" of the methods is not relevant to the instant rejection. Accordingly, it is maintained that in view of the combined teachings of Smith and the Gibco BRL catalog, it would have been obvious for one of skill in the art to utilize the methods of transfecting human ES cells, as taught by Smith, by using a transfection reagent, such as LIPOFECTIN®, with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to make such a modification, as it was an art-recognized goal to optimize transfection techniques of mammalian cells, and, as supported by the Gibco BRL catalog, that the LIPOFECTIN® reagent is a more efficient method of transfecting cells than calcium phosphate or DEAE-dextran transfection methods.

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear and convincing evidence to the contrary.

The prior rejection of claims 1-4, 6, 10, 36, 48, 52, 54 and 56 under 35 U.S.C. 103(a) as being unpatentable over Thomson when taken with Bradley *et al.* is maintained for reasons of record.

Applicants argue that no reasonable expectation of success exists to combine these references exists because others have shown that homologous recombination techniques, known at the time of filing and applied to human ES cells, fail to produce transfected human ES cells. Applicants point to Zwaka and Thomson as evidence for this. See pp. 13-14 of the Response.

This is not found to be persuasive. Zwaka and Thomson state that using a typical mouse ES cell protocol, they were able to transfect human ES cells. The fact that they state that the amounts are "too low to be practical" is not relevant to the instant rejection, because the claims encompass even one hES cell that has been transfected by the described methods. The claims do not have any particular limitation with regard to percentage, concentration or number of cells that would be transfected, nor does the claim require any particular transfection efficiency. Note further that the specification supports that electroporation techniques would be able to produce transfected human ES cells. See p. 11, lines 30-33 and Figure 1.

Accordingly, in view of the combined teachings of Thomson and Bradley, it would have obvious for one of ordinary skill in the art to transfect the human pluripotent stem cells, as taught by Thomson, by the method taught by Bradley, with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification, as supported by Bradley, that transgenic pluripotent stem cells can be easily selected, for example, if they express a selectable marker. See col. 4, lines 26-38.

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear and convincing evidence to the contrary.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Amy Nelson, Acting SPE of Art Unit 1632, at (571) 272-0804. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

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